

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
THIABENDAZOLE

Chemical Code # 587, DPN 242
SB 950 # 341

August 14, 1987

Revised 9/21/89, 12/11/89, 12/20/90, 4/28/92, 6/26/92, 7/22/92, 12/22/92, 1/31/95, 5/18/95, 9/28/95, 1/19/96, 3/7/97 and 12/5/97, 11/17/98 and 12/12/2003

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect [chronic effect, <u>not</u> oncogenicity]
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Teratology, mouse	No data gap, possible adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

All relevant record numbers indexed as of 3/7/97 have been examined. This includes all records up to Record No. 206842 (Document No. 242-107). Some record numbers for this material are of the series 900,000+. Aldous, 3/7/97.

File name: T031212

Present revision by: Gee, 12/12/03

Past updates by: Kellner, 4/28/92 and 6/26/92; Gee, 7/22/92; Kellner, 12/22/92 and 1/31/95; Aldous, 5/18/95, 9/28/95, 1/19/96, 3/7/97 and Gee, 12/5/97, 11/17/98 and 12/12/03.

The chemical grouping includes thiabendazole hypophosphite salt (chemical code # 1952, DPN 50807). See Thiabendazole (chemical code # 587, DPN 242) for reviews.

These pages contain summaries only. Each individual worksheet may contain additional effects.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED RAT

****242-074 129602** Wolfe, G. and Squibb, R. "Thiabendazole: 106-Week Dietary Toxicity/Carcinogenicity Study in Rats." (Hazleton Washington, Inc. (HWA), Vienna, Virginia, Merck Report #TT 90-9009, HWA Project 284-172, 9/29/93). Thiabendazole technical (lot No. L-585, 216-000S159, purity of 98.9%) was administered in the feed to 50 Sprague-Dawley Crl:CD®BR rats/sex/dose at 0, 10, 30 and 90 mg/kg/day for 104 weeks. Body weights and food consumption were decreased in the mid- and high-dose males and high-dose females at most intervals tested. Erythrocyte, hemoglobin and hematocrit levels were decreased in mid- and high-dose rats. Total cholesterol was increased in high-dose rats. Higher liver-to-body weight ratios for high-dose males and higher thyroid/parathyroid-to-body-weight ratio for the high-dose females compared to control were reported. NOEL for systemic toxicity = 10 mg/kg/day.

Possible Adverse Effect: Liver centrilobular hypertrophy in mid- and high-dose males; benign thyroid adenomas (possible mechanism: liver metabolic enzyme induction, leading to increased thyroxine clearance and thyroid stimulating hormone (TSH) levels). Initially classified unacceptable, but upgradeable with submission of data from test compound/dosing mixture analyses. Requested data were provided (Record No. 137480, below). Study is now classified **Acceptable**. Kellner, 1/13/95; Aldous, 9/21/95.

242-085 137480 McKeon, J. F. [untitled report of dosing material analysis for cited study]. Analyses were submitted to support rat combined study: Document No. 242-074, Record No. 129602 (rat chronic/oncogenicity study). Analyses were performed by Merck & Co., Inc. Cover letter with submission was dated May 3, 1995. Stability of technical material was confirmed after study termination (purity of 98.7%). Assay results over the course of the study were within 20% of target in all cases, and generally within a few percent of expected concentrations. Information allows an upgrade of study to **Acceptable** status. Aldous, 9/28/95.

242-070 121292 This supplemental submission is a FIFRA Section 6(a)(2) Adverse Effects Disclosure for Combined (Chronic/Oncogenicity) Rat study -074:129602 concerning increased incidence of benign thyroid adenomas in the 30 and 90 mg/kg/day dose groups. The author stated that increased thyroid adenomas may be the result of a species specific mechanism in which thiabendazole affects the thyroid in the rat indirectly (i.e., alteration of thyroxine clearance via increased hepatic metabolism causing prolonged increase in TSH levels and thyroid follicular cell hyperplasia). No Worksheet. Kellner, 1/27/95.

242-0105 206829 "Thiabendazole: One-hundred-six week dietary toxicity/oncogenicity study in rats TT# 90-9009, HWA Project No. 284-172 (MRID 43593201). Statistical analysis of survival and thyroid tumor data." (Thakur, A. K., Covance Laboratories (formerly Hazleton Washington, Inc., (HWA)), for Syngenta Crop Protection, January 9, 2002) Supplement to 129602. The slightly higher survival at the high dose, 90 mg/kg/day, was not statistically

significant. The tumor incidences were analyzed using several asymptotic and exact statistical methods. No tumors in either sex were considered the cause of death. This supplemental submission gives the incidence of thyroid follicular cell adenomas in males as 3/50, 0/50, 1/50, 5/50 and 6/50, for the two controls groups and 10, 30 and 90 mg/kg groups, respectively. The incidence in the initial report (record 129602) gave the incidence for follicular cell adenomas in male control group I as 0/50. The identity by animal number of the 3 males in the control group I with follicular cell adenomas is requested. No change in status of the study evaluation at this time. (Gee, 12/12/03)

242-0106 206840 "Responses to the draft EPA Registration Eligibility Document (RED) on thiabendazole." (Chukwudebe, A., Human Safety Assessment, Syngenta Crop Protection, Number 2422-01, December 14, 2001) The primary issue in the response of Syngenta regarded the classification of thiabendazole by the CARC of US EPA as "likely to be carcinogenic to humans." The basis for this evaluation by EPA was the incidence of thyroid follicular cell adenomas in male rats. This incidence had a significant trend for adenomas and adenomas/carcinomas combined. Syngenta's response agreed with the significance of the incidence at 30 and 90 mg/kg in males but stated there was no positive trend for carcinomas. Results from a series of *in vitro* and *in vivo* genotoxicity studies were summarized. The response acknowledged that thiabendazole is an inhibitor of tubulin polymerization *in vitro* in fungi but further discussed why this is not relevant to human risk and why several positive studies *in vivo* in animals were flawed. The relationship of thiabendazole to other members of the benzimidazole group, in terms of activity, was discussed. Unlike some others (benomyl, MBC, thiophanate-methyl), thiabendazole does not induce liver tumors, is direct acting, does not contain a carbamate moiety, and is rapidly oxidized to 5-hydroxythiabendazole, followed by conjugation. The roles of TSH, thyroxine, liver metabolism and thyroid hyperplasia were discussed. The quantitative and qualitative differences between rodents and humans were compared. The author concluded that EPA should change the classification to one indicating the "data are inadequate..." for an assessment of human oncogenic potential. No worksheet. (Gee, 12/12/03).

CHRONIC TOXICITY, RAT

See the acceptable rat chronic/oncogenicity study under "combined" studies, above. Note, in addition to laboratory animal studies presented in this summary, the extensive testing and use of thiabendazole in substantial dosages in man and domestic animals as an anthelmintic (see reviews in Vol. 242-012). Aldous, 9/25/95.

** 242-026 036977 (see also related chronic study 242-027 036978) "Safety evaluation by dietary feeding to rats for 104 weeks." (Woodard Research Corp. 12/8/65.) Thiabendazole, lot no. L-585216-0-40 (estimated purity 99.1%), was fed in the diet for 2 years to 35/sex/group at 0, 80 or 120 mg/kg. NOEL (considering information from both related chronic studies) = 40 mg/kg/day. **Acceptable only in fulfillment of chronic effects data requirement--a rat oncogenicity study is still required.** Insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies preclude acceptance for oncogenicity data requirement. DPR reviews by J. Remsen (Gee), 8/22/85 and 1/28/86, did not accept study for chronic or oncogenicity data requirements. Re-examined by C. Aldous on 8/12/87 in light of new data and in consideration of the overall chronic effects data base, and accepted for chronic effects data requirement.

EPA one-liner: No core grade. Systemic NOEL < 80 mg/kg (LDT; growth depression, decreased adrenal weights and increased mortality) Oncogenic NOEL > 120 mg/kg (HDT)

242-012 033541 2-paragraph summary of 026 036977, above. (Review by J. Remsen (Gee), 8/22/85)

242-002 051499 Food consumption data for 026 036977.

242-027 036978 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4/8/64) Thiabendazole, purity 99.1% [from Vol. 002, cover memo and Table 1], was administered in the diet to CD rats for 2 years to 35/sex/group at 0, 10, 40 or 160 mg/kg. Apparent NOEL = 40 mg/kg (decreased body weight). **Unacceptable as an individual study, but contributes to fulfillment of rat chronic effects data requirement (see one-liner for study 026 036977).** As in study 026 036977, there were insufficient numbers of animals subjected histopathology, several required tissues not examined, misc. other deficiencies. DPR reviews by J. Remsen (Gee), 8/22/85 and 1/29/86. Re-examination of data by C. Aldous, 8/12/87.

EPA one-liner: No core grade. Systemic NOEL = 10 mg/kg.

242-012 033540 2-paragraph summary of 026 036978, above. (Review by J. Remsen (Gee), 8/21/85)

242-003 051504 Contains no new rat chronic data. Sections D and E include data on a 6-month rat subchronic study. Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page).

SUBCHRONIC RAT

242-056 087980 Kangas, L., "Thiabendazole: A Fourteen-Week Oral Toxicity Study in the Albino Rat." (Bio-Research Laboratories. Ltd., Laboratory Project I.D. 84114, Study No. TT#89-9014, 1/22/90). Thiabendazole, purity not given, was administered by gavage at doses of 0 (0.5% aqueous methylcellulose), 25, 100, or 400 mg/kg/day to 20 albino rats/sex/group for 14 weeks. No DPR toxicologist's review was required for this subchronic study, however it was noted that the investigators found marked body weight gain decrements in the high dose groups, suggesting that it may be necessary to select a dose level below 400 mg/kg/day for the high dose in subsequent lifetime feeding studies. No adverse effects were noted by investigators, who placed the NOEL at 25 mg/kg/day, based on changes in hematology (i.e., reduced RBC counts, HCT, and Hb.), and on histological changes, such as lesions in stomach mucosa, thyroid follicular cell hyperplasia, and hepatocellular centrilobular hypertrophy. One-liner (without worksheet) by Kishiyama and Aldous, 12/19/90.

242-056 087981 Hill, R. N. et al., "Review: Thyroid follicular cell carcinogenesis." Publ. in Fundam. Appl. Toxicol. 12:629-697 (1989). This review is a discussion of the relationship between thyroid-pituitary homeostasis and eventual development of thyroid follicular cell neoplasms. As of 12/19/90 there is no DPR "review" of this review. Aldous, 12/19/90. Note: A copy of this article was submitted in Document No. 242-085, and was considered in the review of Record No. 137482 in that document (Aldous, 9/28/95).

**** 242-060 096231** "Thiabendazole: A 14-Week Dietary Toxicity Study in Rats." (B. A. Myers

and G. R. Lankas, Merck Sharp & Dohme Research Laboratories [Merck TT# 90-9002], and Hazleton Laboratories America, Inc., [HLA Study No. 284-169], 12/13/90). Thiabendazole, purity 99.4%, was administered in the feed at nominal concentrations of 0, 10, 40, 160 or 320 mg/kg/day to 10 Sprague-Dawley rats/sex/group for at least 13 weeks. Body weight and food consumption was significantly reduced for males and females in the 3 and 2 highest dose groups, respectively. Erythroid parameters were slightly reduced; cholesterol and blood urea nitrogen levels increased for the 2 highest dose groups, but these were considered secondary effects to reduced food consumption and body weight gain. Alopecia was reported to be treatment related (i.e. severity was increased) for the 2 highest dose groups, but only 2 of 10 males and females in each group showed this symptom. Liver centrilobular hypertrophy, thyroid follicular cell hypertrophy and bone marrow erythroid hyperplasia were noted under microscopic examination with a NOEL = 10 mg/kg/day (also for marked decreases in food consumption and body weight in males at 40 mg/kg/day and above). ACCEPTABLE. Dose levels of 10, 30, and 90 mg/kg/day established for a subsequent carcinogenicity study are justifiable. (Kishiyama, Kellner and Gee. 5/1/92).

242-085 137482 Lankas, G. R., "Fourteen-week dietary thyroxine clearance study in rats with a 14-week recovery period." (Merck Research Laboratories, West Point, PA, 2/16/95. Study ID# 94-024-0.) Male Crl:CD®(SD)BR rats, 35/group, were dosed with technical thiabendazole in diets for 14 weeks to achieve 0, 10, 90, or 270 mg/kg/day. Blood was sampled at weeks 2, 4, 8, and 13 to evaluate serum levels of TSH, T3 and T4. After the treatment period, 15 rats/group were necropsied, with histological examinations of livers and thyroids. At this time, an additional 5 rats/dose continued on treatment and were used for pharmacokinetic studies: thyroxine kinetic parameters such as half-life, apparent volume of distribution, and clearance were determined at 8, 22, 34, 48, and 72 hr after iv injection of ¹²⁵I-thyroxine. Remaining rats were taken off treatment for 13 weeks. Serum levels of TSH, T3 and T4 were measured in these rats on recovery weeks 6 and 13. Body weights at the end of the treatment phase were reduced in 90 and 270 mg/kg/day rats by 12% and 32%, respectively. There were similar decrements in food consumption at these dose levels. Respective TSH levels between weeks 8 and 13 were 170% and 198% of control levels. There were no effects on T4 levels. T3 levels of 270 mg/kg/day rats were slightly lower than controls, however this may have been incidental, considering lack of effects on T4 concentrations. Relative liver weights were increased at 270 mg/kg/day, and absolute and relative thyroid weights were elevated at 90 to 270 in dose-related fashion. Liver centrilobular hypertrophy and thyroid follicular cell hyperplasia commonly occurred at 90-270 mg/kg/day. Investigators noted that ¹²⁵I-thyroxine clearance (units of ml/hr) was remarkably increased at 270 mg/kg/day, and that the main factor behind this change was a great increase in apparent volume of distribution at this dose. Investigators also considered this elevated clearance to be the reason for the compensatory increase in TSH. The DPR review contends that this study does not clearly demonstrate enhanced liver metabolism of thyroid hormones as the sole or primary cause for the TSH response, considering factors such as the effects of inanition on hormonal balance, and confounding effects of marked metabolic, physiological and anatomical treatment effects upon pharmacokinetic parameters. Aldous, 9/28/95.

CHRONIC TOXICITY, DOG

Studies 242-027 036979 and 242-012 033542 have been previously considered together to fill the chronic dog data requirement. Subsequently Record No. 123765 has been reviewed and classified **acceptable**. Aldous, 3/7/97.

****242-072 123765** Lankas, G. R. "Thiabendazole: Fifty-three week oral toxicity study in dogs." (Merck Institute for Therapeutic Research, West Point, PA. Laboratory ID: TT #91-968-0, 1/20/93.) Beagles were dosed with 0, 10, 40, or 160 mg/kg/day thiabendazole (identified as L-585,216-000S159, purity approximately 99%) by gelatin capsule for 1 year. Neither NOEL nor NOAEL was found. Vacuolation of the gallbladder epithelium was present in dose-related degree in both sexes at all doses. The death of one 40 mg/kg/day male early in the study was considered by investigators to be a possible idiosyncratic treatment effect. There were no comparable reactions in either sex at that dose or above. [A dose of 50 mg/kg/day has been used for years routinely as an anthelmintic for dogs and other animals]. Common findings at 40 mg/kg/day included liver bile duct vacuolation and urinary bladder epithelial cytoplasmic inclusions. A noteworthy reduction in RBC parameters in high dose dogs was associated with other indications of anemia, especially bone marrow hematopoiesis at 160 mg/kg/day and splenic erythropoiesis and/or hemosiderosis at 40 and 160 mg/kg/day. No adverse effects are indicated. Study was originally classified as unacceptable, due to lack of information about test article purity and stability. Requested data were submitted as part of a rebuttal, dated 9/25/95 (see also 3/7/97 DPR rebuttal response). Study is re-classified as **acceptable**. H. Green and C. Aldous, 5/18/95; Aldous, 3/7/97.

242-072 123795 Smith, P. F. et al., "Studies on the mechanism of simvastatin-induced thyroid hypertrophy and follicular cell adenoma in the rat." Publ. in Toxicologic Pathology 19:197-205 (1991). This article was included in the dog chronic study report (Record No. 123765) to demonstrate how induction of hepatocellular metabolic activity can lead to increased turnover of thyroid hormones, and subsequently to thyroid follicular hypertrophy. This has been considered already with respect to thyroid changes in the rat (see previous pages, this Summary). No worksheet for this article. Aldous, 4/26/95.

242-027 036979 "Safety Evaluation by Oral Administration to Dogs and Rats for 104 Weeks." (Woodard Research Corp., 4/8/64) Thiabendazole, technical., purity 99.1%, was administered to beagles, 3/sex/group, by capsule 5 days/week at 0, 20, 50 or 125 mg/kg. Apparent NOEL = 20 mg/kg/day ("mild lacrimation and scleral injection" noted at 50 mg/kg/day and above: salivation, rough hair coats, dry skin, reduced hemoglobin and hematocrit, seizures and some mortalities at 125 mg/kg/day (the latter two findings not necessarily direct treatment effects.)) J. Remsen (Gee), 1/29/86; C. Aldous 8/6/87.
EPA one-liner: No core grade. Systemic NOEL = 50 mg/kg (decreased body weight).

242-012 033543 Very brief summary of 242-027 036979, initially reviewed by J. Remsen on 8/22/85.

242-002 051500 Individual body weights for 027 036979.

242-012 033542 "Two Year Chronic Oral Toxicity in Dogs." (Merck Sharp and Dohme Research Labs, 1-69) [Summary report]. Thiabendazole, technical. 99.1%, was given to beagles daily for 2 years at 0, 20, 100 or 200 mg/kg, 2/sex/group [doses were raised to above levels by degrees to prevent emesis of dose]. Interim sacrifices of one control and one 200 mg/kg/day male 5 months after 200 mg/kg/day treatment began. Apparent NOEL = 20 mg/kg/day (Hemosiderosis of liver and bone marrow at 100-200 mg/kg/day; reduced body weights, also reduced RBC counts, hematocrits, and hemoglobin at 200 mg/kg/day. Not an acceptable independent report, but useful data considering supplementary information, below. J. Remsen (Gee), 8/22/85; subsequent review with ancillary data by C. Aldous, 8/6/87.

242-003 051505 (Tab = "Section D", relevant pages are D-205 through D-297) provides data for study 012 033542. Data include individual food and water consumption, hematology, clinical chemistry, prothrombin time, urinary output, body weights, and organ weights. Body weights appear to be reduced in 200 mg/kg/day dogs, however there was no mortality. Males and females in the 200 mg/kg/day group appeared to have reduced RBC counts, hematocrits, and hemoglobin concentrations compared to all other groups. In tab marked "Section E" there were tables 15-19, indicating results of microscopic examination of dogs in the 1969 study, 012 033542. The only consistent apparent treatment effects were marked to moderate hemosiderosis in liver and bone marrow in 100 and 200 mg/kg/day groups (both sexes). Section G is a duplicate of the entire contents of Vol. 027 (differs only in the placement of one page). (Ancillary data only. See overall review of this study and of 027 036979, summarized above, worksheet by C. Aldous, 8/6/87).

SUBCHRONIC DOG

242-055 087979 Batham, P. "Thiabendazole. A Fourteen-Week Oral Toxicity Study in the Beagle Dog." (Bio-Research Laboratories. Ltd., Laboratory Project. I.D. 84021, Study No. TT#89-9010, 1/22/90). Thiabendazole, purity 99.4%, administered orally via gelatin capsule at doses of 0 (placebo capsule), 35, 75, or 150 mg/kg/day to 4 beagle dogs/sex/group for 90 days. Incidence of emesis (NOEL = 35 mg/kg/day) and salivation increased; erythrocyte parameters (RBC, Hb, and HCT) decreased. It appears that the dosage range employed in this study would be appropriate for a subsequent chronic study, should such a study be undertaken. Note that studies 242-027 036979 and 242-012 033542 together have already fulfilled the chronic dog data requirement for DPR. The information from this subchronic study is supplementary. (Kishiyama and Aldous, 12/19/90, one-liner without worksheet).

ONCOGENICITY, RAT

Journal Article (no document or record #): Fuji, T. et al. 1991. "Chronic Oral Toxicity and Carcinogenicity Study of Thiabendazole in Rats." Publ. in Fd Chem. Toxic., Vol. 29, No. 11, pp. 771-775. Thiabendazole (TBZ, purity of 98.5%, obtained from Merck Sharp and Dohme International, NJ) was administered in the diet at nominal concentrations 0, 500, 1000, 2000 or 4000 ppm to 30 F344/DuCrj rats/sex/dose for 104 weeks. Body-weight gain was reduced about 20 and 40% compared to controls in the 2000 and 4000 ppm dose groups, respectively. Survival of rats was enhanced with increasing dose level. Lung phagocytes (foamy cells) showed significantly increased focal or multifocal aggregation at 1000 ppm and above in females and 2000 ppm and above in males. Liver bile duct hyperplasia with periductal fibrosis increased in a dose-related manner in females but not males; hepatic microgranuloma showed dose-related increases in both sexes. Hyperplasia of renal tubule and collecting duct epithelium of the kidney was seen in high-dose males and females; hyperplasia of the epithelium of both the papilla and pelvis of the kidney was significantly higher in the 2000 and 4000 ppm dose groups of both sexes. NOEL for hyperplasia of kidney papilla and pelvis epithelium is 500 ppm (21 mg/kg/day in males, 26 mg/kg/day in females). **Possible Adverse Effect:** Preputial (male) and clitoral (female) gland adenomas were increased at the high dose, NOEL = 2000 ppm (male: 90 mg/kg/day). Not a guideline study; supplemental data only. Kellner and Gee, 5/4/92.

242-048 067761 and 242-051 074912 are based on the same study described in the preceding one-liner (Fuji, et al., 1991). Specifically, -048 067761 is a journal article (Hayashida et al.,

1985. Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health 36, pp. 377-389) that was published before the pathologic examinations were completed and is consequently lacking these data. It does contain weekly body weight, food and water intake, hematology, serum biochemistry and organ weight data that were not included in the 1991 paper. Study -051 074912 is an unpublished, draft version of the pathology report; it also contains additional details not found in the 1991 article (e.g. lesion counts for all examined organs are listed). Kellner and Gee, 6/29/92.

242-051 074911 "Enhancing effect of thiabendazole by urinary bladder carcinogenesis induced by sodium o-phenylphenate in F344 rats." (T. Fuji et al. (1986), Food and Chemical Toxicology, 24(3):207-211. This is paper from the open literature. No worksheet was done (Morris, 10/13/89).

ONCOGENICITY, MOUSE

**** 242-025 036966** "Lifetime Carcinogenic Study in Mice," (Merck, Sharp & Dohme, 1/2/80). Thiabendazole (purity = 99.3 - 99.8%) was administered to CD-1 mice (50/sex/group) in the diet at 0 (vehicle = 1% vegetable oil in the diet), 0.006, 0.066 and 0.20% (males) or 0.006, 0.200, and 0.533% (females) [low dose groups were initiated at higher levels, but adjusted to above levels at week 7]. Animals in a group were sacrificed when survival reached 20% (81-105 weeks). **Possible adverse effect indicated: (atrial thrombosis).** NOEL = 0.006% (i.e. 60 ppm or about 5.7 to 9.9 mg/kg/day (female) or 0.066% (660 ppm or about 63-121 mg/kg/day (male), based on increased mortality in both sexes dosed at $\geq 0.20\%$ in diet, due primarily to atrial thrombosis). Note: NOEL for males was incorrect in earlier review (see discussion in 9/21/88 review). No oncogenic effect indicated. This study was originally reviewed by J. Gee (1/30/86) as unacceptable but upgradeable, with a possible adverse effect (apparent increase in "Type B" hepatocellular tumors in 0.533% females). Study was re-examined by C. Aldous (8/11/87) and still considered to be unacceptable, but upgradeable upon receipt of additional information to clarify the statistical and toxicological meaning of the apparent increase in hepatic "Type B" neoplasms. The requested information (046:064610, which included "blind" re-evaluation of slides by R. A. Squire) removes the concern about possible hepatocellular tumors (no treatment effect seen on secondary review). Study is upgraded to ACCEPTABLE. C. Aldous and M. Silva, 9/21/88.

EPA one-liner: Minimum. Oncogenic NOEL > 0.533% (HDT) systemic NOEL = 0.066% (lower weight gain).

242-046 064610 Additional information relating to study 025 036966. Definition of Type A and Type B hepatocellular tumors and interpretation of significance of data in the original report. Historical control data on such tumors. Report of "blind" secondary evaluation of female liver slides by R. A. Squire, who found no evidence of treatment effect on tumors. One-page EPA memo, which indicated that EPA had determined that there was no oncogenic effect (following evaluation of Squire report and independent evaluation of slides by EPA). See DPR review of 9/21/88 for details. C. Aldous, 9/21/88.

242-012 033544 Summary of 025 036966, above, reviewed by J. Remsen (Gee) 8/22/85.

342-002 051501 (Addendum to 025 036966) "Thiabendazole: Six-week pilot study in mice." ([TT #77-004-0]. Merck Institute for Therapeutic Research, 8/24/77.) Thiabendazole

mixed in diet to provide daily doses of 0, 50, 150, 300, 600, and 900 mg/kg/day. Males had slight decrease in food consumption and body weight gain at 600 and 900 mg/kg/day. No changes in females. This study justifies the dose levels used in the primary study. D. Shimer/ C. Aldous, 7/11/87. [Note that C. Aldous requests additional information relating to the primary study.]

REPRODUCTION, RAT

**** 242-028 036980** "Multigeneration Reproduction and Lactation Studies with Thiabendazole." (Food and Drug Research Labs, 12-26-67). Thiabendazole, purity approx. 98.8%, administered orally in diet (in very young rats) or by gavage (in older rats) from mating through weaning to FDRL rats at 0, 20, 40 or 80 mg/kg; 10/sex/group; NOEL > 80 mg/kg for reproduction; no effect on reproduction parameters. Originally classified as "unacceptable" in reviews of J. Remsen (Gee) [8/22/85 review of the summary of this report in 012 033547, and 1/29/86 review of final report in 028 036980]. Re-evaluated by D. Shimer/ C. Aldous on 8/10/87, and found **ACCEPTABLE**, on basis of additional data in 002 051502 (see below).

EPA one-liner: No core grade. Reproductive NOEL = 20 mg/kg (decreased viability index of F1A). [Note that DPR does not agree with this determination, as there is no consistent treatment effect on viability or on other reproductive parameters].

242-012 033547 Brief summary of 242-028 036980 (see above).

242-002 051502 (Addendum to Document 028 036980, above). Explanation of dosing regime (part gavage, part dietary admixture), purity information (approx. 98.8% purity, process same as in current production), individual reproduction data, hematology, clinical chemistry, and organ weights for adults, reproduction and lactation data. These data allow upgrade of principal study to upgradeable status. D. Shimer/C. Aldous, 7/10/87,

****242-066 116221** "Two-Generation Dietary Reproduction Study in Rats." (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Thiabendazole (>99% purity) was administered in the diet through two generations with 1 litter per generation at nominal concentrations of 0 (control), 10, 30, and 90 mg/kg/day and with 33 and 25 Sprague-Dawley [CrI:CD®(SD) BR] rats/sex/dose for F0 and F1 parents, respectively. Prior to mating, F0 and F1 adults received treated diet for approximately 9-weeks and 14-weeks, respectively. Group mean F0 and F1 parental body weight reduction (7% to 14%) and food consumption decrease (8% to 16%) was indicated at 90 mg/kg/day. Significantly decreased pup weight gain was seen at 90 mg/kg/day. Parental NOEL = 10 mg/kg/day (reduced body weights and food consumption at 30 and 90 mg/kg/day). Reproductive NOEL = 30 mg/kg/day (reduced pup weights at 90 mg/kg/day). **No Adverse Effects. Originally unacceptable, but upgradeable** [with analyses of test compound (with verification of technical grade) and dosing material]. (Green, Kellner and Gee, 11/10/92). Test compound/dosing mixture analyses (see -071:122339) have been submitted and the study is upgraded to **ACCEPTABLE**. Kellner, 1/31/95.

-071 122339 Addendum to -066 116221 "Two-Generation Dietary Reproduction Study in Rats." (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Supplemental submission included information on the analysis of the test compound and results of the dietary

analyses conducted during the study. Although not conducted under GLP standards (see - 075:129603), these analyses were adequate to establish that the rats received their prescribed dosages; study -066:116221 is upgraded to ACCEPTABLE. Kellner, 1/31/95.

-075 129603 Addendum to -066 116221 "Two-Generation Dietary Reproduction Study in Rats." (Dr. L. David Wise, Merck Institute for Therapeutic Research, Merck Research Laboratories, Merck & Co., Inc., West Point, PA. Report # TT #90-733-0, 21 May 1992). Supplemental submission included changes inserted into to final report which were the result of a U.S. EPA GLP inspection. These additions had no effect on either the final conclusion of the report or the DPR evaluation of the study. Kellner, 1/30/95.

242-030 036981 "Thiabendazole Evaluation of Teratogenic Potential in the Rat." [Study is actually a 1-generation reproduction study]. (Woodard Research Corporation, 4/8/64) Thiabendazole, no purity stated, was given at 0 or 500 ppm in the diet for 70 days, 20/sex/group, 2 litters raised to weaning. NOEL > 500 ppm for 1 generation reproduction study. No adverse effect indicated. UNACCEPTABLE, inadequate protocol. J. Remsen (Gee), 1/29/86. Re-examined after receipt of 002 051503 (see below) by D. Shimer/C. Aldous, 7/10/87.

242-012 033546 Brief summary of the 1-generation, 2-litter reproduction study, reported more fully in 030 036981, above. This summary reviewed by J. Remsen (Gee) on 8/22/85, and found UNACCEPTABLE.

242-002 051503 (Addendum to 030 036981) New data are individual body weights of pups at birth and at 21 days. No changes in interpretation of study. Report is now complete, and study remains UNACCEPTABLE. D. Shimer/C. Aldous 7/10/87.

REPRODUCTION, MOUSE

242-012 033545 "Reproduction and Teratogenic Studies: Multigeneration Reproduction Study in the Mouse." (Merck Sharp and Dohme Research Labs, 1-69) Brief summary of a 5 generation study in which thiabendazole was administered in the diet to 25/sex/group at 0, 0.02, 0.1 or 0.5 % of diet. Reproductive effects NOEL = 0.1% in diet (reduced numbers of mice born and weaned per litter, reduction of weanling weight). (**Note:** 8/22/85 review by J. Remsen (Gee) considered reproductive effects at 0.5% in diet to be a "possible adverse health effect". This dose was shown to be well into the toxic range in the mouse oncogenicity study (242-025 036966, which found increased mortality in males dosed with 0.066% and higher concentrations in diet and in females dosed 0.20% and above, also decreased body weight gain in both sexes at 0.200% and above). Reviewer (Aldous) therefore determines that **reproductive effects at this high and parentally toxic level do not constitute a "possible adverse health effect"**. (Report remains UNACCEPTABLE (no data provided). (Re-reviewed by C. Aldous, 8/14/87.)

EPA one-liner: No core grade. Reproduction NOEL = 150 mg/kg.

TERATOGENICITY, RAT

** 242-059 096230 "Thiabendazole: Oral Developmental Toxicity Study in Rats." (L. D. Wise, Merck Sharp & Dohme Research Laboratories, Project I.D. No. TT# 90-713-0, 11/16/90.) Thiabendazole, purity 98.9%, was administered by gavage at doses of 0 (0.5% methy-

lcellulose), 10, 40, or 80 mg/kg to 25 mated Sprague-Dawley female rats per group on days 6 through 17 of gestation. Body weights of high-dose maternal rats ranged from 1.7% to 4.8% less than control at day 8 and 14 of gestation, respectively; food consumption during dosing was reduced 11-15% and 22-28% for the mid and high dose groups, respectively. Maternal NOEL = 10 mg/kg/day, based on reduced body weight gain and food consumption. Fetal body weight was significantly lower and averaged 4.9% and 6.3% less than controls for mid and high dose males, respectively, and 4.7% lower for high dose females. **No Adverse Developmental Effects.** Developmental NOEL = 10 mg/kg/day, based on reduced fetal weights. Initially reviewed as unacceptable but upgradeable (Kishiyama, Kellner and Gee, 5/1/92). Upgraded to **acceptable** with submission of -068:117129. (Kellner and Gee, 11/3/92).

242-068 117129 [Addendum to -059:96230] Supplemental submission provided analytical method and tabulated results of dosing material analysis for upgrade of rat teratogenicity study (-059:96230) to acceptable. Kellner and Gee, 10/29/92.

242-046 064612 "Report on Prenatal Toxicity Studies in Rats with Thiabendazole," (Institut für Pharmakologie, Toxikologie und Pharmazie, 8/14/85). Thiabendazole (analytical grade, no purity given; Ch. RMO 5878, Batch No. 18295 supplied by MSD) was administered in diet to mated Wistar SPF rats at 0 (vehicle = diet), 2, 15, 50 and 100 ppm during days 6-17 of gestation (presence of vaginal plug = day 0 of gestation). **Maternal NOEL > 100 ppm** (no significant effects were observed at any dose level). **Possible adverse effect indicated. Developmental NOEL = 15 ppm** (significantly lower fetal weights at 50 ppm (3.5 g) and 100 ppm (3.4 g) compared with 3.6 g in controls; significant increase in major malformations in the skeletal system at 100 ppm). NOT ACCEPTABLE (no analysis of test chemical; no analysis of dosing material was included; individual maternal food and water consumption data and fetal visceral, skeletal, external effects and bodyweights were missing; no GLP or QA was included; an "annex" section was cited but missing from the report; historical controls should have been included with the study). Possibly upgradeable (the above mentioned missing information must be submitted to DPR). M. Silva, 9/7/88.

242-046 064611 "Thiabendazole - Review of Available Rat Teratology and Fetotoxicity Studies." In this report a number of studies are summarized, including 064611-12, 064615 and 064622. Other studies (Delaour et al.) were mentioned where one dose was tested on Sprague-Dawley rats and no developmental or maternal effects were noted at 80 mg/kg/day (gavage). Two studies performed at the Institute of Pharmacology and Toxicology in Hanover West Germany (Wistar Rats treated by gavage) were briefly described. Dose levels were: Study 1. 100, 200, 400 and 800 mg/kg/day and Study 2. 200 (15 mg/kg), 400 and 800 ppm. NOELs were not reached in the German studies and fetal effects (13% weight reduction) were observed at the lowest dose levels tested -100 mg/kg/day (maternal effects were not mentioned) in Study 1. **Both maternal and developmental effects were observed in Study 2 at 200 ppm (15 mg/kg/day)** but since a NOEL was not reached, indications of adverse effects cannot be determined. Based on the data presented in the summary, fetotoxic effects are secondary effects due to decreased weight gain in dams (maternal toxicity). It is not conclusive whether TBZ is teratogenic or selectively fetotoxic. This information is supplementary. M. Silva, 9/6/88.

242-046 064615 "Effect of Dietary Administration of Thiabendazole on Pregnant Rats and Fetal Development," (J. Food Hyg. Soc. Japan, Vol. 23, No. 6, pp. 468-473, 1982). Thiabendazole (> 98% pure) was given in diet to mated Wistar rats at 0 (vehicle = diet), 0.125 (92 mg/kg), 0.25 (154.5 mg/kg), 0.5 (223.7 mg/kg) and 1% (187.5 mg/kg, calculated to be less

due to reduced food consumption in the 1% group) during days 7 to 17 of gestation (positive vaginal smear = day 0 of gestation). Maternal NOEL = 0.125% (maternal body weight gain and food consumption were significantly suppressed at $\geq 0.25\%$; clinical signs of toxicity, included piloerection, listlessness/general weakness were observed at $\geq 0.5\%$). Developmental NOEL = 0.125% (decreased body weight at $\geq 0.5\%$; increase in incidence of fetal death at 1%; increased skeletal variations at $\geq 0.5\%$; retardation of ossification at $\geq 0.25\%$). There was no evidence of fetal malformations attributable to thiabendazole ingested. Fetal changes were considered to be primarily induced by direct effects of thiabendazole on the fetuses as well as effects due to maternal weight loss brought on by a marked decrease in food consumption. No adverse effect indicated. This information is supplementary. M. Silva, 9/7/88.

242-046 064622 "Teratologic Assessment of Maleic Hydrazide and Daminozide, and Formulations of Ethoxyquin, Thiabendazole and Naled in Rats." (*J. Environ. Sci., Health*, B14(6), pp. 563-577, 1979). Mated (positive vaginal smear = day 1 of gestation) Wistar rats were treated by gavage with 0 (vehicle = distilled water), 125, 250 or 500 mg/kg thiabendazole (formulation = 45% a.i. & 55% unknown ingredients) during day 6-15 of gestation. Maternal NOEL ≥ 500 mg/kg (no effects were observed at any dose). No adverse effect indicated. Developmental NOEL = 500 mg/kg (although an increase in the total number of anomalous fetuses/number of fetuses examined in the 500 mg/kg group was observed ($P < 0.005$), no single anomaly was significantly increased in incidence). This information is supplementary. M. Silva, 9/7/88.

Summary: The definitive studies are -046:064612 and -059:096230. In 064612, a possible adverse effect with a developmental NOEL of 15 ppm was demonstrated (significantly decreased fetal weights at 50 and 100 ppm and increased skeletal malformations at 100 ppm), but the study was found to be unacceptable by DPR because of numerous deficiencies. A guideline-type study (-059:096230) has since been reviewed with a conclusion of no developmental effects in fetuses other than lower body weight with a NOEL of 10 mg/kg/day (equal to the maternal NOEL). This study was originally found to be unacceptable, but was upgraded to acceptable after review of supplemental submission -068:117129. This guideline study will be used to establish the NOEL for rat teratogenic effects. (Kellner and Gee, 11/9/92).

TERATOLOGY, RABBIT

** 242-062 097879 "Thiabendazole: Oral Development Toxicity Study - Rabbits." (G. L. Lankas & L. D. Wise, Merck Sharp & Dohme Research Laboratories, Project ID Number TT # 90-734-0, 6/10/91). Thiabendazole (lot Number L585, 216-000S159), purity 98.9% (based on TLC) was administered by oral gavage at concentrations of 0 (0.5% methylcellulose), 50, 150, or 600 mg/kg to 18 mated female New Zealand Rabbits/group during gestation days 6 through 18. **Developmental NOEL = 150 mg/kg/day** (increased resorptions, lung lobation, incompletely ossified metacarpal and reduced fetal weight for the high dose group). Increases in incompletely ossified sternebra and talus-calcaneus were reported to be within the historical control range. **Maternal NOEL = 150 mg/kg/day** (based on decreased body weight gain and food consumption during the treatment period). The "possible adverse effects" flag was removed from the rabbit developmental toxicity test because **no adverse developmental effects** were seen below maternally toxic doses. Initially reviewed as unacceptable but upgradeable (Kishiyama, Kellner and Gee, 5/1/92); study was upgraded to **Acceptable** with submission of -068:117130. (Kellner and Gee, 11/3/92).

242-068 117130 [Addendum to -062:97879] Supplemental submission provided analytical method and tabulated results of dosing material analysis for the upgrade of a rabbit teratogenicity study (-062:97879). In addition, historical control data and information from previous studies were presented that allowed the developmental NOEL to be increased from 24 mg/kg/day (as recommended in previous rabbit study -054:90065) to 150 mg/kg/day (from study -062:97879), thus permitting removal of the "possible adverse effect" flag from the rabbit developmental toxicity test. Kellner and Gee, 10/29/92.

Note: One of the purposes of study TT #90-734-0 (-062 97879) was to clarify the relationship of thiabendazole treatment to the occurrence of fetal hydrocephaly, resorptions and abortions seen in the mid- and high-dose treatment groups (120 and 600 mg/kg/day) of study TT #89-9005 (-054 90065). In the latter study, the NOEL for developmental toxicity was 24 mg/kg/day based on whole litter resorptions and hydrocephaly. The NOEL for maternal toxicity (120 mg/kg/day) was based on decreased body weight gain and food consumption. The study indicated a **"possible adverse effect"** based on embryo-fetal toxicity in the absence of definitive maternal toxicity. In contrast, study TT #90-734-0 showed a single case of hydrocephaly at the low dose only and no definitive adverse developmental effects at 50 mg/kg/day.

A supplemental report (-068:117130) was submitted by the author to explain the differences in results between the two studies and to provide justification for a maternal and developmental NOEL of 150 mg/kg/day. For example, data were presented which showed that the frequency of skeletal malformations reported in the first study was comparable to historical control data. Further evidence was presented in the form of thiabendazole range-finding study in which 8 pregnant does received doses of either 200 or 400 mg/kg/day under the same conditions as the first study; no evidence of adverse developmental effects was reported. These and other data allowed the developmental NOEL to be increased from 24 mg/kg/day to 150 mg/kg/day, thus permitting removal of the "possible adverse effect" flag from the rabbit developmental test.

****242-054 090065** Hoberman, A. M., "Thiabendazole: Oral Developmental Toxicity Study in Rabbits." (Argus Research Laboratories Inc., project No. 013-029; Merck & Co., Inc. study number: TT89-9005, October 27, 1989). Thiabendazole, purity 98.9%, administered by gavage at doses of 0 (0.5% methylcellulose), 24, 120, or 600 mg/kg/day to 18 artificially inseminated Hra: (New Zealand White) SPF rabbits/group on days 6 through 18 of gestation. Maternal toxicity NOEL = 120 mg/kg/day (marked body weight gain decrements, marked decrease in food consumption during treatment). Developmental toxicity NOEL = 24 mg/kg/day [4/18 litters with whole litter resorptions at 120 mg/kg/day; also hydrocephaly in 2 fetuses (2 litters) at 600 mg/kg/day and 1 fetus at 120 mg/kg/day]. The study technically indicates a **"possible adverse effect"**, based on embryo-fetal toxicity in the absence of definitive maternal toxicity. ACCEPTABLE. (Kishiyama and Aldous, 12/19/90).

242-054 090066 Rangefinding study for Record #090065, above. Dosage levels selected for the above primary study are justified. No DPR worksheet for the pilot study, which is addressed in the review of the primary study. This 1-liner is by Aldous, 12/19/90.

242-030 036982 Entitled "Thiabendazole reproduction [sic] study in the rabbit" (actually a teratology study). (Merck Institute for Therapeutic Research, June 29, 1966.) Doses of 100, 200, 400, and 800 mg/kg/day by gavage in Methocel® suspension. No adverse effects indicated. Not complete, NOT ACCEPTABLE, upgrade unlikely (intercurrent disease, small group sizes, small numbers of fetuses subjected to skeletal examinations, etc.). Original review

by J. Remsen (Gee), 1/29/86, [Not acceptable, possible upgrade indicated], subsequent review by C. Aldous considering additional information (below), 8/12/87, [NOT ACCEPTABLE, unlikely upgradeability].

242-002 (No record #, rebuttal on pp. 9-10 at front of volume). Addendum to study 030 036982. Identifies test article as purity of approx. 99.1%, comparable to currently manufactured product. Clarifies that data from 4 small studies conducted within 5 months were combined into one report. Indicates that individual data are available on request. No change in status of study indicated. Aldous (considered in 8/12/87 review, see above).

TERATOGENICITY, MOUSE

****242-089 140365** Nakatsuka, T., "Thiabendazole: Oral developmental toxicity study in mice." (Banyu Pharmaceutical Co., Ltd. (Japan), 6/26/95, Study ID Number TT #94-9818.) Thiabendazole, purity 99.8%, was administered via gavage at doses of 0 (olive oil), 25, 100 or 200 mg/kg/day to 25 Jcl:ICR mice/group during days 6 through 15 of gestation. Maternal NOEL = 25 mg/kg/day [weight gain decrements, (very marginal at 100 mg/kg/day)]. Fetal NOEL = 25 mg/kg/day (small, dose-related decrements in mean fetal weight). A "possible adverse effect" is indicated, based on incidence of cardiovascular malformations at 200 mg/kg/day. This is based on 2 high dose litters with such changes, compared to 1 fetus each in low and medium dose groups, and none in controls. Study investigators did not consider data to indicate teratogenicity. Kishiyama and Aldous, 1/19/96.

242-089 140358 Pilot study for Record No. 140365, above. Dams were dosed by gavage on gestation days 6-15 at 25, 100, 200, 400, and 800 mg/kg/day. There were modest b.w. decrements at 400 and 800 mg/kg/day, and modest reductions of the major hematology parameters at these dose levels (i.e. reduced RBC counts, Hb, and HCT). Live fetal weights were reduced statistically significantly in dose-related fashion over the dose range of 100 mg/kg/day and above. An increase in incidence of cleft palate at 800 mg/kg/day (15 fetuses, 4 litters) was attributed to treatment, possibly mediated by maternal stress. Dose levels selected for the definitive study are consistent with findings in this pilot study. Aldous, 1/19/96.

Journal Article (No Document or Record #). Ogata, A. et al. "Teratogenicity of Thiabendazole in ICR Mice." (Fd. Chem. Toxic. Vol. 22, No. 7, pp. 509-520. Dept. of Toxicology, Tokyo Metropolitan Research Laboratory of Public Health, Japan.) Thiabendazole (TBZ, 98.5% purity, lot no. A101) was administered in olive oil orally to pregnant mice at different stages of organogenesis (3 experiments). Experiment 1: 39 mice/dose were given daily doses of 0, 700, 1300 or 2400 mg/kg/day on days 7-15 of gestation. Experiment 2: 7-12 mice/dose were given a single dose of 2400 mg/kg on one day during days 6-15 of gestation. Experiment 3: 22-31 mice/dose received one of a range of 17 dose levels between 30 and 2400 mg/kg on day 9 of gestation.

In exp. 1, maternal deaths numbered 5/39 and 24/39 in the two highest dose groups; fetuses showed dose-related external and skeletal anomalies (e.g., cleft palate and fusion of vertebrae).

In exp. 2, at least one maternal death occurred on each treatment day; dose-related reduction deformity of the limbs was found in mice given 2400 mg/kg on one day 9-12.

In exp. 3, maternal deaths occurred in doses exceeding 1389 mg/kg; increasing dosage of TBZ led to proportional increases in the number fetuses with reduction deformity of limbs and skeletal fusion. The effective dose (ED₁) for skeletal fusion of 26 mg/kg was established by probit analysis.

Although the methods, results and conclusions described in the article were scientifically sound, this study was not performed under FIFRA GLP guidelines; these data should be considered supplementary only. A key limitation of the study was that internal soft tissue examinations were not undertaken. (Kellner and Gee, 4/17/92)

GENE MUTATION

** 242-067 116350 "Thiabendazole Microbial Mutagenesis Assay." (Joseph F. Sina, Ph.D., Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Report Numbers TT# 91-8039 and TT# 91-8042, 4 March 1992). Thiabendazole (>99.5% estimated purity by TLC) was tested with and without metabolic activation in the reversion assay using Salmonella typhimurium (TA97a, TA98, TA100, and TA1535) and Escherichia coli (WP2, WP2 uvrA, and WP2 uvrA pKM101) plated in quadruplicate with 48 hour exposure at nominal concentrations of 0, 3, 10, 30, 100, 300, 1000, 3000, and 6000 ug/plate. **Increased reversion frequency was not indicated. Acceptable.** (Green, Kellner and Gee, 11/6/92).

** 242-029 036968 and 036969 "Mutagenicity Testing on Thiabendazole in Microbial Systems." (The Institute of Environmental Toxicology, report no. 76-9814C, no date) Thiabendazole, >98.6%, was tested with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100 and G46, *E. coli* strain WP2 hcr-, with and without rat liver activation at 0, 10, 100, 500, 1000 and 2500 ug/plate. No increase in mutagenicity was observed. **ACCEPTABLE.** (J. Gee, 1-28-86)

EPA one-liner: Acceptable. Negative, no increase in G46 revertants from mice exposed to TBZ.

242-029 036976 "Thiabendazole: Microbial Mutagenicity Studies (Ames Test) with *Salmonella typhimurium*." (Merck, 1977, report no. 76-9813C) Several lot numbers of thiabendazole were tested with *S. typhimurium* at 0 to 2000 ug/plate, with and without phenobarbital induced rat liver enzymes. Data demonstrate that the low level mutagenic activity in TA98 was due to an impurity in lot #F291764. No adverse effect indicated. **UNACCEPTABLE.** (J. Gee, 1/28/86)

EPA one-liner: Acceptable. Negative for induced revertants in all Ames strains except TA98 + phenobarbital S-9.

242-012 033551 "Mutagenic Studies: Host Mediated Assay - *Salmonella typhimurium* in Male ICR Mice." (Merck Sharp and Dohme Research Labs, 1-69, report no. 76-9814C) Summary report states no significant increase in mutation frequency of *Salmonella* strain G46. **UNACCEPTABLE.** (J. Gee, 8/22/85)

242-012 033662 "Mutagenic Studies: in vitro Bacterial Mutagen Tests - Reverse Mutation Tests - *E. coli*." (Merck Sharp and Dohme research Labs, 1-69) Single sentence states no increase in *E. coli* revertants. **UNACCEPTABLE.** (J. Gee, 8/22/85)

242-012 033549 "Mutagenic Studies: in vitro Bacterial Mutagen Tests-Ames Tests." (Merck Sharp and Dohme Research Labs, 1-69, report no. 76-9813C) *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without Aroclor-induced rat liver activation.

Paragraph states no mutagenic activity found up to 2.5 and 5.0 ug/plate. UNACCEPTABLE. (J. Gee, 8/22/85)

No record number. A *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. @ E. Zeiger, B. Anderson, S. Haworth, T. Lawlor and K. Mortelmans in: Environmental and Molecular Mutagenesis, 11 (Supplement 12): 1-158 (1988). Thiabendazole (98-99%0 was one of the chemicals tested at SRI with *Salmonella* strains TA98 and TA100 using preincubation for 20 minutes before plating. Concentrations used were 0 (DMSO), 100, 333, 666, 1666, 3333, 6666 and 10,000 µg/[plate with and without hamster or rat liver activation at different percentages. Both were Aroclor 1254-induced. Precipitate formed at 1666 µg/plate and higher. Results were judged by the authors as negative for TA100 but positive with 10% and 30% hamster liver activation with TA98 with a concentration dependent increase in colonies in the presence of precipitate. Activation with rat liver (30%) gave negative results with TA 98. Possible adverse effect. Summary data. No worksheet. (Gee, 11/16/98).

SUMMARY: There is no evidence for mutagenicity of thiabendazole in bacteria but there is a suggestion that an impurity in some lots may be weakly mutagenic in at least one strain of *Salmonella* - TA98 - for frameshift mutation. [DPR reviewer name not stated: may have been J. Gee on or about 1/28/86].

CHROMOSOME EFFECTS

****242-078 131712** "Thiabendazole: Assay for Chromosomal Aberration in Mouse Bone Marrow." (Sheila M. Gallaway, Merck Institute for Therapeutic Research, West Point, PA., 11 July 1994). The test article is identified as thiabendazole (TBZ) with 99.8% purity. Eight, 10, or 12 male Crl:CD-1®(ICR)BR mice per group received a single dose of 0, 200, 667, and 2000 mg/kg by gavage, with mitomycin C as the positive control. Sampling was performed at 6, 24, and 48 hours post-treatment. Increased chromosomal aberrations are not indicated at the levels tested. Study was initially classified as unacceptable but upgradeable (adequate justification for 1 sex only, test article verification as technical grade). Requested data were submitted as part of a rebuttal, dated 9/25/95 (see also 3/7/97 DPR rebuttal response). Study is re-classified to **acceptable**. H. Green and J. Gee, 5/18/95; Aldous, 3/7/97.

**** 242-029, 047 036971, 067211-12** "Cytogenetic Studies With Thiabendazole in Rat Bone Marrow Cells." (Institute of Environmental Toxicology, Tokyo, Japan; report no. 76-9816C, no date). Thiabendazole (purity = 98.6%) was given by oral gavage as a single dose at 0, 100, 300 or 1000 mg/kg or 5 doses at 30, 100 or 300 mg/kg (5 males/group). Animals were sacrificed at 24 hours (single dose) and 3 hours (5 doses). No increase in bone marrow chromosomal aberrations are reported. The study was originally reviewed as unacceptable (J. Gee, 11/28/86) but upgradeable with justification of use of males only instead of both sexes as required. The requested information was received at DPR (047 067211) and based on the fairly complete data base which indicated no sex differences in any of the tests, the study has been upgraded to **ACCEPTABLE**. (M. Silva, 9/9/88)

EPA One-liner: Acceptable. Negative for chromosome damage in rat bone marrow cells.

242-049 067759 Exact duplicate of 047:067212.

242-012 033555 Summary of 029 036971.

242-047 067213 "Selected Mutagenesis Studies on Thiabendazole," (SRI International, 3/77). Thiabendazole (purity and grade not specified) was used on human diploid fibroblast WI-38 cells in the log phase of growth at 0 (vehicle = 1% DMSO), 0.1, 1.0, 10.0, 100 and 1000 ug/ml without activation duplicate samples. No increase in chromosomal aberrations was observed at any concentration level. Positive controls functioned as expected. UNACCEPTABLE (purity of test material was not provided nor was an analysis of dosing material; the test was not run with enzyme activation; only one time point was sampled; QA statement not included). Not upgradeable. (M. Silva, 9/9/88)

242-029 036970 "Cytogenetic Studies with Thiabendazole in Cultured Human Fibroblasts." (Institute of Environmental Toxicology, report no. 76-9815C, no date.) Thiabendazole, 98.6%, was tested with human embryo fibroblasts, strain #1162, for *in vitro* chromosomal aberrations; exposed to 0, 2, 10 or 50 ug/ml for 3 and 24 hours, no activation, no increase in aberrations. UNACCEPTABLE. An activation system must be used. (J. Gee, 1/28/86)
EPA one-liner: Acceptable. Negative - no increase in chromosome breakage in human embryonic fibroblast cultures.

242-012 033553 Summary of 029 036970.

242-012 033554 "Mutagenic Studies: Cytogenetic Studies - in vitro Studies with Human Diploid Fibroblasts." (Merck Sharp and Dohme Research Labs, 1-69) WI-38, 3 hour exposure. Summary report states a depression in mitotic index but no increase in aberrations. UNACCEPTABLE. (J. Gee, 8/22/85)

242-029, 047, 049 036972, 067211, 067760 "Dominant Lethal Studies With Thiabendazole in Mice," (Institute of Environmental Toxicology, 76-9817C, no date). Thiabendazole (purity = 98.6%) was administered by gavage to C3H/HeCr mice (15 males/group) at 0, 200 or 600 mg/kg for 5 consecutive days. No adverse effect indicated. NOEL > 600 mg/kg for dominant lethal effect. Originally reviewed as unacceptable by J. Gee, 1/28/86 (no individual data; no analysis of dosing material; no justification of dose and dosing schedule). Justification for dose selection (range-finding study: 049 067760) was submitted to DPR, however, results of the preliminary study do not justify the final dose selection. The study remains UNACCEPTABLE and not upgradeable. (M. Silva, 9/9/88)

EPA one-liner: Not acceptable. Negative for dominant lethals in treated C3H/HeCR mice.

242-029 036974 "Thiabendazole: Mutagenicity Study in the Mouse Using the Micronucleus Test." (Merck, 6/3/77, report no. 76-8-83). Thiabendazole, lot no. F291764 (no purity stated), was administered by oral gavage to 8 (or 14 for control)/sex/group CD-1 mice at 0, 125, 250 or 500 mg/kg/day, 2 doses; sacrificed at 6 hrs; NOEL > 500 mg/kg; no effect on micronucleus in PCE's or PCE/NCE reported. UNACCEPTABLE. Doses are not justified, protocol is unacceptable, no purity stated. (J. Gee, 1/28/86)

EPA one-liner: Not Acceptable. Negative (up to 500 mg/kg) in CD-1 mice.

242-012 033552 Summary of 029 036974.

242-029 036975 "Thiabendazole: Mutagenic (Subacute Dominant Lethal) Study in the Mouse." (Merck, 1977, report no. 76-7030) Thiabendazole, lot no. F291764 (no purity stated), given by oral gavage to 10 CF₁S males per test group (20 for negative control), at 0, 125, 250 or 500 mg/kg/day in 5 daily doses; NOEL for dominant lethal > 500 mg/kg; mated over 8 weeks,

1:1, no adverse effect reported. UNACCEPTABLE. No justification of doses, no concurrent positive control or appropriate historical data, not enough females per time point. (J. Gee, 1/28/86)

EPA one-liner: Not acceptable. Negative (up to 500 mg/kg) in CF1S mice.

242-012 033557 Summary of 029 036975.

242-012 033556 "Mutagenic Studies: Dominant-Lethal Studies - C3H/HECR Mice." (Merck Sharp and Dohme Research Labs, 1-69) Summary report, 200 and 600 mg/kg given in 5 doses, **no effects noted over 6 weeks of mating**. No data. UNACCEPTABLE. (J. Gee, 8/22/85)

242-029 036975 "Thiabendazole: Mutagenic (Subacute Dominant Lethal) Study in the Mouse." (Merck, 1977, report no. 76-7030) Thiabendazole, lot no. F291764 (no purity stated), given by oral gavage to 10 CF, S males per test group (20 for negative control), at 0, 125, 250 or 500 mg/kg/day in 5 daily doses; NOEL for dominant lethal > 500 mg/kg; mated over 8 weeks, 1: 1, no adverse effect reported. UNACCEPTABLE. No justification of doses, no concurrent positive control or appropriate historical data, not enough females per time point. (J. Gee, 1/28/86)

EPA one-liner: Not acceptable. Negative (up to 500 mg/kg) in CF1 S mice.

242-012 033557 Summary of 029 36975.

242-012 033556 "Mutagenic Studies: Dominant-Lethal Studies - C3H/HECR Mice." (Merck Sharp and Dohme Research Labs, 1-69) Summary report, 200 and 600 mg/kg given in 5 doses, **no effects noted over 6 weeks of mating**. No data. UNACCEPTABLE. (J. Gee, 8/22/85)

No record number. "Micronucleus test of polyploidy inducers." (Ohuchida, A. et. al. In: Mutation Research 216: 371-372 (1989)). This is an abstract with no data. Thiabendazole was one of 5 chemicals tested in male BDF1 mice by ip injection. All were in vitro polyploidy inducers. No dose levels were reported. MNPCes were analyzed at 24, 48 and 72 hours. The abstract states that there was no increase in MNPCes. UNACCEPTABLE. No worksheet. (Gee, 11/16/98)

No record number "Thiabendazole-induced cytogenetic abnormalities in mouse oocytes." (Mailhes, J. B., D. Young, M. J. Aardema and S. N. London, Environmental and Molecular Mutagenesis 29: 367 - 371 (1997), laboratories of Proctor and Gamble and Louisiana State University, 1/30/97) Thiabendazole (> 99%) was given by ip injection to ICR female mice at doses of 0 (DMSO), 50, 100, 150 and 200 mg/kg. Doses were selected based on a preliminary study. The doses were administered to mice immediately after injection ip of 5.0 IU human chorionic gonadotropin to induce ovulation. Oocytes were harvest 17 hours after treatment with thiabendazole and processed for cytogenetic analysis. Several experiments (number not specified) were conducted to collect enough oocytes for analysis. Discrimination between intact dyads and single chromatids was done by C-banding. The number of ovulatory mice, MI and MII cells, MII cells with polyploidy (n = 30 - 40), hypoploidy, haploidy and hyperploidy were determined. Results showed that treatment with thiabendazole decreased the number of ovulatory mice with increasing dose for 50 mg/kg and higher. Nonovulatory mice in the controls were 6.6% (2/30) while with treatment, the percentages were 24.4 (11/45), 20.0 (11/55), 51.7 (77/149) and 74.5 (41/55) respectively. In addition, the average number of oocytes per ovulatory female decreased at 150 and 200 mg/kg (0: 29.4; 50: 27.1; 100: 23.2; 150: 15.8***; 200: 7.7***). The MI: MII ratio was not affected by treatment. The frequency of hyperploid (n 20 1/2 - 29 Y2) oocytes was statistically increased at 100 mg/kg (1.3*) compared to control (0) but not at 50 or 150 mg/kg. This value of 1.3 was slightly outside the range of historical control values (0 - 1.2 with an average of 0.2) and was interpreted to

suggest that thiabendazole is "at most a weak aneugen *in vivo* There were an insufficient number of oocytes at 200 mg/kg to be evaluated. The study was unacceptable based on summary data and is SUPPLEMENTAL. (Gee, 11/19/98)

No record number. "Mutagenic bioassay of certain pharmacologic drugs. 1. Thiabendazole (TBZ)." (Mudry de Pargament, M. D., M. Labal de Vinuesa and 1. Larripa, Mutation Research 188: 1 - 6 (1988), laboratories of Academia Nacional de Medicina, Buenos Aires and Centro Austral de Investigaciones Cientificas, Tierra del Fuego, accepted 11/27/86) Thiabendazole (no purity given) was tested in three assays, two *in vivo* in CFW mice and one *in vitro* with CHO cells. The doses selected were based on human therapeutic dosages given as an antihelminthic. The low dose, 50 mg/kg, was considered half the TD, 100 mg/kg, the TD and 200 mg/kg, DD or double the dose. **Sister chromatid exchange:** Male mice were injected twice with BrdU ip 9 h apart with thiabendazole (0 (water), 50, 100 or 200 mg/kg, 3/dose group) given ip 30 min before the second BrdU injection. Colchicine was injected 9 - 12 hours after the second BrdU injection and the mice sacrificed 2 hours later. Bone marrow cells were processed and 20/male mouse examined for SCEs. A statistical increase in SCE/cell at 200 mg/kg (4.2 compared with 3.2) was reported. The effect was considered to occur at DD for therapy. No increase was seen at either 50 or 100 mg/kg - **Micronucleus assay:** Male and female mice were injected ip with these same doses (single dose) and sacrificed 30 hours later. Bone marrow smears were stained and a minimum of 1000 polychromatic erythrocytes per animal examined. The positive control was AMSA [4'-(9-acridinylamino)methanesulfonamidide]. The frequencies of micronuclei at all three doses of thiabendazole were statistically increased over controls (14.9, 16.8 and 20.0 for sexes combined versus 8.2) but were not different from each other. The conclusion of the authors was that thiabendazole is a direct mutagen producing clastogenic effects. **In vitro assay:** CHO cells were exposed to 0, 0.06, 0.12, 0.24 or 0.6 ug/ml for 24 hours immediately after subculturing. AMSA was the positive control. Details of the method were not given. Normal and abnormal (bridges, multipolars) were scored in 100 cells per culture (no details). At 0.24 and 0.6 ug/ml, a statistically significant increase in abnormal anaphases (primarily in bridges) were found. Control: 6.5%; 0.24: 17%; 0.6: 23% with positive control value being 54%. The authors concluded that the effects were positive due to altered microtubules with subsequent malfunction of the spindle apparatus. **Possible adverse effects.** Unacceptable due to summary status in a publication. SUPPLEMENTAL. (Gee, 11/19/98)

No record number. "Mouse micronucleus tests with known and suspect spindle poisons: results from two laboratories." (L.-D. Adler, Kliesch, U., van Hummelen, P. and KirschVolders, M., Mutagenesis 6: 47 - 53 (1991)) Thiabendazole was one of 10 chemicals tested in each of two laboratories in Neurenberg (Lab. 1) and in Brussels (Lab. 2). Lab. 1: Male and female (1 02/EI x C3H/EI) F1 mice were injected with 125, 250, 375 or 500 mg/kg and sacrificed at 6 and 24 hours, 5/sex/dose group/time. Micronuclei in 2000 polychromatic erythrocytes of bone marrow were scored. Lab. 2: Swiss albino mice were injected with 640 mg/kg and sacrificed at 24 and 48 hours, 3/sex/time. 1000 PE were scored. Both laboratories concluded that thiabendazole did not induce the formation of micronuclei in mouse bone marrow erythrocytes. **UNACCEPTABLE** (summary data) No worksheet. (Gee, 11/24/98)

DNA DAMAGE

242-029 036967 "Mutagenicity Testing on Thiabendazole in Microbial Systems." (The Institute of Environmental Toxicology, 76-9813C, no date.) Thiabendazole, >98.6%, was tested

with *Bacillus subtilis* strains H17 and M45 at 0, 2, 10, 20, 50, 100, 200, 500 and 1000 ug/disc, no metabolic activation, no adverse effect indicated. UNACCEPTABLE, not upgradeable.

Metabolic activation must be used. (J. Gee, 1/28/86)

EPA one-liner: Negative. No differential toxicity between *B. subtilis* strains H17 and M45.

242-012 033550 Summary of 029 036967.

** 50807-006 074699 "Thiabendazole, In Vitro Alkaline Elution/Rat Hepatocyte Assay." (Merck Institute for Therapeutic Research, West Point, PA., Study # 89-8312, 5/19/89), Thiabendazole, MK-0360, 98.9% purity. Primary rat hepatocytes, isolated from Charles River CrI:CD®(SD) BR Sprague-Dawley rats, were exposed to 0, 0.3, 0.7, 1.0, or 1.3 mM (in 1% DMSO) for 3 hours and analyzed for DNA strand breaks by the alkaline elution method. Viability was ≥ 93 % of controls.

Elution rates were less than 3 times controls indicating no adverse effect. The study is acceptable. (H. Green, S. Morris, 10/13/89).

NEUROTOXICITY

Not required at this time.

OTHER

242-031 036983 "Chronic toxicity study of thiabendazole in volunteers." (Colmore, J. P., Moore, J. D. and Worley, W. E., University of Oklahoma and Merck Sharp & Dohme Research Laboratories, NDA 16-096, 1965) One hundred male volunteers from the Oklahoma State Penitentiary were given thiabendazole (125 mg capsule twice daily, 250 mg/day) or a placebo. Dosing continued for six months. Age ranged from 20 to 60 years. Laboratory tests included clinical chemistry (glucose, alkaline phosphatase, cholesterol, prothrombin time, clotting time, BUN, serum bilirubin), urinalysis and ECG. Subjects were interviewed weekly with physical examinations at 1, 3 and 6 months. Laboratory tests were conducted at 4th, 12th and 24th weeks.

Of the 100, 77 completed the study with 12 completing 12 or more weeks. Reasons for not completing the study included parole and disciplinary action. No subject developed significant changes in physical condition, and blood pressure and pulse were unaffected. Increased appetite was the most frequently reported effect. There were no laboratory findings clearly associated with thiabendazole at 250 mg/day over 24 weeks. No worksheet. [See the Risk Characterization Document for thiabendazole, August 10, 2001, for further information regarding this study.] (Gee, 12/12/03)

242-0107 206842 "Chronic toxicity study of thiabendazole in volunteers." Partial duplicate of 036983 above. Submitted by Syngenta as number 2549-01. (Gee, 12/12/03)